

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P04-095PCT	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/JP2004/009384	International filing date (day/month/year) 25.06.2004	Priority date (day/month/year) 26.06.2003
International Patent Classification (IPC) or national classification and IPC		
Applicant TAISHO PHARMACEUTICAL CO., LTD.		

<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>6</u> sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> (sent to the applicant and to the International Bureau) a total of _____ sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>																									
<p>4. This report contains indications relating to the following items:</p> <table border="0"> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. I</td> <td>Basis of the report</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>		<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input type="checkbox"/>	Box No. II	Priority	<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input type="checkbox"/>	Box No. VIII	Certain observations on the international application
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Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/JP	Authorized officer
Facsimile No.	Telephone No.

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Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language _____ which is the language of a translation furnished for the purposes of:
- ☐ international search (Rule 12.3 and 23.1(b))
- ☐ publication of the international application (Rule 12.4)
- ☐ international preliminary examination (Rule 55.2 and/or 55.3)
2. With regard to the elements of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):
- ☒ the international application as originally filed/furnished
- ☐ the description:
- pages _____ as originally filed/furnished
- pages* _____ received by this Authority on _____
- pages* _____ received by this Authority on _____
- ☐ the claims:
- nos. _____ as originally filed/furnished
- nos.* _____ as amended (together with any statement) under Article 19
- nos.* _____ received by this Authority on _____
- nos.* _____ received by this Authority on _____
- ☐ the drawings:
- sheets _____ as originally filed/furnished
- sheets* _____ received by this Authority on _____
- sheets* _____ received by this Authority on _____
- ☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages _____
- ☐ the claims, nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to sequence listing (*specify*): _____
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages _____
- ☐ the claims, nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to sequence listing (*specify*): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>2-23</u>	YES
	Claims	<u>1, 24, 25</u>	NO
Inventive step (IS)	Claims	<u></u>	YES
	Claims	<u>1-25</u>	NO
Industrial applicability (IA)	Claims	<u>1-25</u>	YES
	Claims	<u></u>	NO

2. Citations and explanations (Rule 70.7)

Document 1: JP 2000-86597 A (F. Hoffmann-La Roche AG.),
28 March 2000, claims and examples 28, 30
and 31

Document 2: WO 02/68380 A1 (Eli Lilly and Co.), 06
September 2002, claims

Document 3: JP 2001-525825 A (Eli Lilly and Co.), 11
December 2001, claims

Document 4: JP 2000-500754 A (Eli Lilly and Co.), 25
January 2000, claims

Document 5: JP 2000-336071 A (Taisho Pharmaceutical Co.,
Ltd.), 05 December 2000, claims and
paragraphs [0004] and [0104]

(1)

The invention set forth in claims 1, 24 and 25
lacks novelty and does not involve an inventive step in
the light of document 1 cited in the international search
report.

The invention set forth in claims 2 to 4 and 6 does
not involve an inventive step in the light of document 1
cited in the international search report.

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Document 1 indicates that (1S, 2R, 3S, 5R, 6S)-2,3-diamino-bicyclo [3.1.0] hexane-2,6-dicarboxylic acids are ligands for group II metabotropic glutamate receptors, and indicates that said compounds are useful for regulating the functions of the receptors in question.

Meanwhile, the group of compounds that is set forth in the present application includes the compounds that are disclosed in document 1; therefore, the effects that are ascribed to the invention set forth in the present application by the applicant in the written opinion do not affect the findings in relation to the novelty of the inventions in question.

In addition, a person skilled in the art could have attempted to substitute an R structure for the asymmetric carbon in position 3 which bonds to the amino group, as appropriate, and the invention in question cannot be considered to exhibit a particularly unexpected effect as a result of substituting in an R structure.

(2)

The invention set forth in claims 1 to 25 does not involve an inventive step in the light of documents 1 to 5 cited in the international search report.

Document 1 indicates that 2-amino-bicyclo [3.1.0] hexane-2,6-dicarboxylic acid derivatives with a substituent group such as an amino group or an alkoxy group in position 3 are ligands for group II metabotropic glutamate receptors, and indicates that said compounds are useful for regulating the functions of the receptors in question.

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement

Meanwhile, the compounds that are set forth in the present application differ from the compounds that are disclosed in document 1 in the light of the structures of the substituent groups in position 3.

However, documents 2 to 5 disclose 2-amino-bicyclo [3.1.0] hexane-2,6-dicarboxylic acid derivatives that have the same activity and the same skeleton as the derivatives that are disclosed in document 1, and further indicate that groups with the same structures as the substituent groups in position 3 of the compounds set forth in the present application can be substituted into position 4 of the compounds that are disclosed in documents 2 to 5. In addition, documents 2 and 5 in particular indicate that it is possible for the substituent group in position 4 of the compounds disclosed therein to be the same alkoxy groups as the substituent groups in position 3 of the compounds disclosed in document 1 in addition to the groups with the same structure as the substituent groups in position 3 of the compounds set forth in the present application; therefore, it would have been easy to infer that it is possible for the substituent groups in positions 3 and 4 of a 2-amino-bicyclo [3.1.0] hexane-2,6-dicarboxylic acid to have similar structures. In other words, it would have been easy for a person skilled in the art to conceive that the substituent groups in position 3 of the compounds that are disclosed in document 1 will not lose their activity even if substituted into position 4 of the compounds that are disclosed in documents 2 to 5.

Furthermore, the compounds that are set forth in the present application may have fluorine in position 6 of the 2-amino-bicyclo [3.1.0] hexane-2,6-dicarboxylic

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acid. However, document 5 presents experiments in which fluorine was bonded to position 6 of compounds with a 2-amino-bicyclo [3.1.0] hexane-2,6-dicarboxylic acid skeletons like those of the compounds that are disclosed in document 1 in order to increase the absorption characteristics, the metabolic stability and the pharmacological effects thereof; therefore, it would not require significant creativity for a person skilled in the art to attempt to bond fluorine to position 6 of the compounds that are disclosed in document 1, as appropriate.

In the written response, the applicant asserts that it was impossible to predict whether the compounds from the invention set forth in the present application would exhibit an inhibitory activity. However, it would have been easy for a person skilled in the art to deduce that the 2-amino-bicyclo [3.1.0] hexane-2,6-dicarboxylic acid structure is associated with the inhibitory activity in the light of the disclosures of documents 1 to 5, and the compounds from the invention set forth in the present application cannot be considered to exhibit a particularly unpredictable inhibitory activity in comparison to the compounds that are disclosed in documents 1 to 5. Therefore, said assertions by the applicant have no affect upon the findings in relation to the inventive step of the inventions in question.